The human circadian clock entrains to sun time

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Supplemental Data:

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Supplemental Experimental Procedures

Chronotype: When two oscillators synchronise, they oscillate with the same period and they adopt a distinct phase relationship to each other [S1]. When circadian clocks are synchronised (entrained) by periodic signals from their environment (zeitgebers, e.g., light or temperature) their phase relationship to the zeitgeber cycle is called chronotype. An example relevant to this work is the temporal relationship between wake time and dawn in humans under natural conditions. Chronotype depends on several properties [S2] such as the strength of the zeitgeber (e.g., how intense the light is during the day and how dark it is at night), and its duration (photoperiod). Chronotype also depends on the endogenous period of the individual circadian clock and on its sensitivity to the zeitgeber stimulus. Furthermore, both the period of the circadian clock and its sensitivity to light are subjected to genetic variation. Individuals, therefore, adopt different phase relationships to the natural light-dark-cycle, i.e., have different chronotypes.

Assessment of chronotype and its normalisation: We assess human chronotype with the help of a simple questionnaire [S3] which essentially determines when people fall asleep and wake up on work days and free days. As a first approach to determining chronotype, the mid-sleep time on free days is calculated (MSF). We use mid-sleep because individual timing of sleep and individual sleep duration are independent traits [S3] which makes both sleep onset and wakeup unreliable markers for sleep timing. In addition, mid sleep correlates best with melatonin profiles and the morningness-eveningness score [S3, S4]. Although MSF is a good indicator of chronotype, sleep deprivation during the work week can act as a confounder for the sleep duration on free days (sleep compensation), leading to a later MSF [S3]. These excessive free-day sleep times are, therefore, corrected for according to the individual's (weekly) average sleep need ($MSF_{sc,}$ for correction algorithm, see supplement to [S5]). Like for MSF, the dimension of MSF_{sc} is not a score; it's dimension is local time and it represents an excellent predictor for the chronotype of an individual's present stage. However, for genetic and epidemiological studies, two additional corrections are applied. Chronotype depends on age, and this age-related change further depends on sex [S5]. These two confounding factors are, therefore, also used for normalisation. Figure S1 shows the age dependencies of female and male subjects based on our present data base (N=40,000). The individual curve fits to the sex-specific datasets are used to calculate a theoretical chronotype (MSF_{sasc}) which is standardised to the age of 30 and corrected for sex-differences (see circle in the supplementary figure). Fits are calculated separately for the delaying and the advancing portions of the age-dependencies, and also separately for males and females (the shift from later to earlier chronotype for females is 19.5 years and for males, it is 21 years) considering ages up to 78. All fits are highly significant (young females: r=0.99; adult females; r=0.98; young males: r=0.99; adult males: r=0.99). Normalisations are performed by adding the difference of a subject's chronotype from the age- and sex-specific mean to MSF_{s30}.

Statistics: Multiple regression analysis, incorporating all data (N=21,600), shows that both longitude and population size are significant <u>and</u> independent predictors of chronotype ($r^2 = 0.017$; $p<0.001$; standardised beta for longitude with population size held constant: -0.108; standardised beta for population size with longitude held constant: 0.129). Using a comparison of slopes method based on the Student's t-test [S6], we determined that the slopes for the different population groups as shown in panels B and C are significantly different with $p<0.01$.

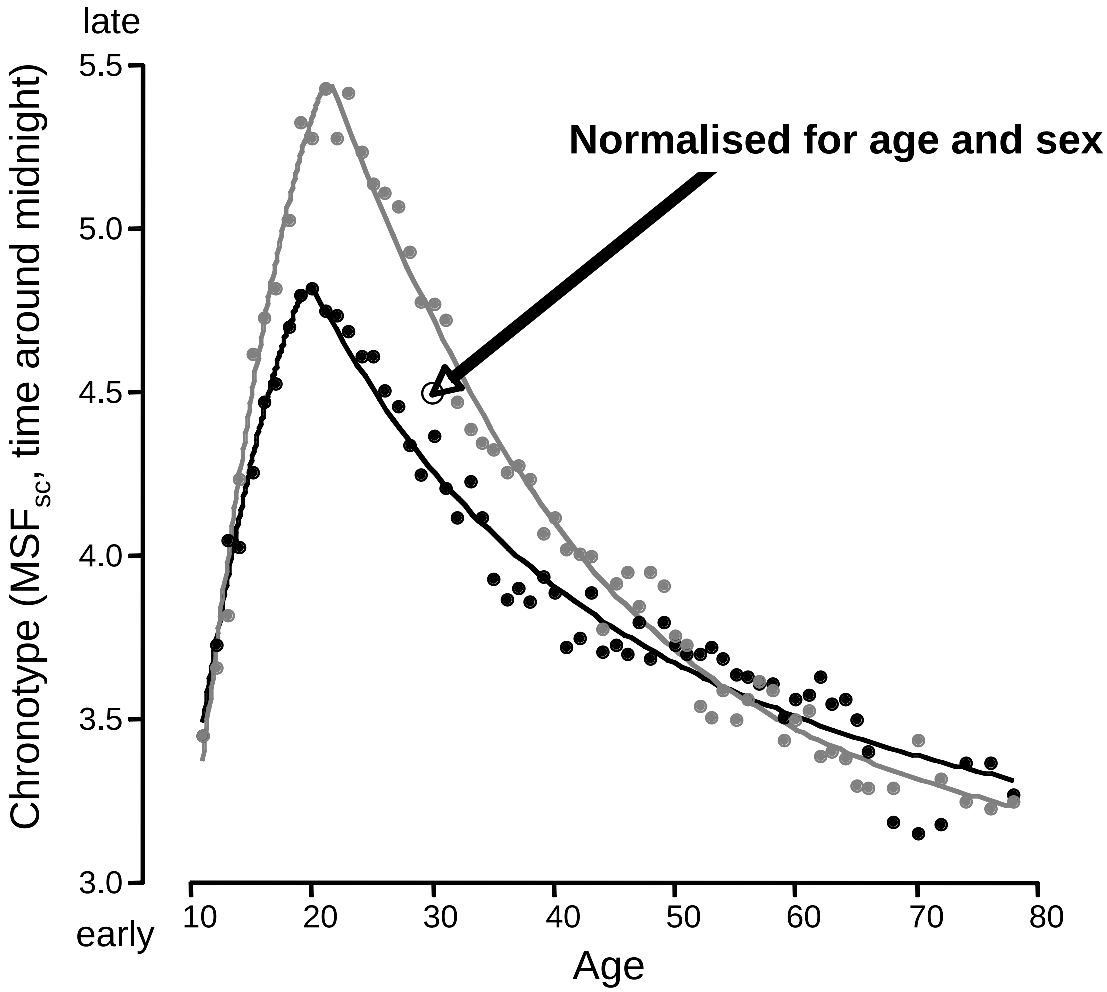

Figure S1: Age-dependent changes in average chronotype are highly systematic and are different for males and females (black: females, grey: males). The open circle represents the average chronotype at the age of 30, corrected for sex-differences (for normalisation procedures, see text).

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